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A tribute to François Gros, a founding father of molecular biology

Sixty years of life with François Gros

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Abstract. This is meant to be a personal account of my relationship with François Gros who, as the director of the laboratory where I had my first team became a close and fatherly friend. Over 60 years we had permanent interactions, whether close or far away. And I wish to revive here some of our relation at the grassroots, as well as the folklore in and around his laboratory. He was not only an excellent scientist but also a Statesman of Science and beyond. Myself a minor figure in his big endeavors, this aspect of his life I just observed from below but with much empathy. All along he considered our experimental data and ideas realistic while they were rejected as iconoclastic by the many others. Being taken seriously as a researcher, I did not participate in his professional networks because I never fit the necessary profile in terms of scientific consensus. But his friendship was a major and basic element in my scientific and personal life; I hope my report hereafter does justice to his personality and immense merits.

Keywords. François Gros, 60 years collaboration, Personal account, Friendship.

Note. This article follows a symposium held on 25 April 2023 at the Institut Pasteur in tribute to François Gros.

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Our collaboration started in 1963 when I came to Paris, after a postdoc at MIT, invited to start a team working on animal cells in François' laboratory at the Institut de Biologie Physico-Chimique (IBPC), at that time fully devoted to bacterial genetics and the phage systems of *E. coli*. In the years to come our relationship evolved slowly, from the "boss" and guide in science to a fatherly friend. Thus, I was also able to follow—indirectly—many of his social undertakings: at the CNRS—which he had helped to found—then the 1968 revolution in his laboratory and the streets, furthermore in 1981 his participation in the Mauroy government. Later on, in 2016, we had organized around him a working team attempting to attract the interest of the candidates of the 2017 French Presidential Election for a strong program in fundamental research, a necessary basis for innovation. When he was in Paris, we met regularly in his cozy office at the Academy of Sciences followed by a short lunch in a nearby *bistro*; on special occasions we also met at Danièle's or our home table.

The first time I met François was at a Gordon conference in 1962. Swimming in a New Hampshire lake I met Ekke Bautz, a German scientist; we found that both of us spoke "Shwezerduetsh" (Swiss), he being from Konstanz, the historical German city south of the Rhine River close my Swiss hometown of Schaffhausen. Shortly after, a young French lady joined us on a solitary rock, mid-lake, closely followed by an MIT professor, "Cy" Levinthal, with whom I collaborated in Jim Darnell's laboratory. When presented to *Madame Françoise Gros*, I asked her—shyly—if she might introduce me to her husband François Gros, the famous scientist from the Institut Pasteur. By chance he already had read my paper—just published in 1962 in *BBRC*—about the discovery of "giant RNA", longer than any RNA then known. And right away he offered me a job in his laboratory—in Paris! France! Immediately I decided to accept, giving up jobs proposed by Alfred Gierer in Tübingen and Wilhelm Bernhard in Villejuif. And I introduced to him my spouse Jutta from

Berlin, studying Russian intellectual history with the protopope of the Russian Orthodox Church of Boston who was also a professor at Harvard; she was enchanted to return to a big city and not a German “village”—like Tübingen.

François was about to set up his laboratory at IBPC. Thus my work started at the Institut Pasteur in his home laboratory directed by André Lwoff—a very “Russian Kniaz”. There, I had the chance to be with François Jacob at the regular lab meetings, and also with Jacques Monod, whom I met once in his office in the company of Agnès Ullman, a refugee scientist from Hungary. Hearing that I was looking for a flat, she proposed that I take over the room where she had stayed with her husband in the apartment of another Françoise. Situated at the passage de la Visitation, on one side it looked over the lush gardens of the Banque de France and on the other side (ours) into a ventilation shaft.

Fortunately, we could soon move to a 25m² former servants’ flat on 33 avenue de Breteuil, where the fancy front apartments were occupied by American postdocs—some from Pasteur. There we received François for the first time, for a Swiss fondue. On arrival he said: “Oh — comme j’aime cela !” It took 30 years before he would admit that he hated fondue: his memory of people and facts was phenomenal!

Pasteur turned soon into the IBPC, the Institute still shielding the spirits of J. Perrin, P. Joliot and *Madame* M. Curie, as well as their former collaborators. Being an architect’s son, I found the red brick building on the rue Pierre (still without Marie) Curie quite curious looking, having lots of small terraces and gardens shielded visually from each other. In a satellite block, François’ group occupied various floors of a staircase, to which our labs were attached. The elegant entry salon, with fancy green fauteuils and a sofa, soon had to be converted into the place for liquid scintillation counters.

Top and bottom floors were still occupied by the department of “Physiologie Animale”. On most sunny afternoons the elderly animal caretaker used to carry a folding chair into a cozy green patio, on which an older lady would rest for hours, right next to the (empty) dog cages. She was the owner of the unused labs I had spotted; François managed to get those labs along with the dog cages—to be soon occupied by my ducks. Genetically pure (obligation for phage genetics!) Pekin ducks imported se-

cretly from Prof. Benoit’s huge animal farm in Orsay. He was on fighting terms with all of Jacques Monod’s microbial genetics clan, having claimed that DNA of brown ducks injected into eggs of white Pekin produced hybrid phenotypes—considered impossible at that time! Poor Benoit, he lived too early; a fate that I later had to appreciate myself—for current science, my iconoclastic ideas came ever 10 years too early.

Indeed, already in Jim’s lab I had come across a particular type of giant RNA which was AU-rich and not GC-rich as the more abundant preribosomal RNA. In view of this base composition and its processing properties, I soon suggested calling it “messenger-like RNA” (not “DNA-like”, as it was asymmetrical in base composition). To get me started, François handed me over some frozen duck blood cells brought by Irving London from Boston, suggesting that I prepare its DNA and determine its base composition and capacity to sustain transcription by the first purified RNA polymerase, gotten straight from Jerry Hurwitz’ laboratory. I found, fortunately, that the astounding incapacity of DNA from (transcriptionally silent) erythrocytes, compared to that from active erythroblast, was due to a contaminant I could eliminate by Bentonite. And I could convince François to go back to “my” giant RNA.

Thus we started to study in detail the more than 10 kb-long RNA that I had observed at MIT. First with Irving London and soon with Lise Marcaud from the Shapira lab, we did pulse-chase experiments on the nucleated duck erythroblasts which, because they were not dividing, produced little pre-rRNA—in contrast to the human HeLa cells. They allowed us therefore to determine the base composition of giant non-ribosomal RNA. This was not straightforward to do, but at least it was possible; thanks to the living ducks surviving the “united front” of *E. coli*, in contrast to the gentle human HeLa cells (a local colleague: “Cultiver des cellules humaines — en suspension ? Impossible, mon cher !”); provided you took a shower after having chased the huge beasts through their living quarters.

And almost every second noon I chewed a juicy “Jambon de Campagne” sandwich at *Chez Père Guimard*, in company of another collaborator of François, the vice-director of the Institut du Radium, François Zajdela, who discovered the function of the nucleoli as the site of ribosomal biosynthesis. He

taught basic cytology to the chemist while getting back some molecular biology. Coming from austere ETH (the Swiss Institute of Technology), I was sort of an odd fellow. “Vous êtes suisse ? Mon pauvre — c’est pas drôle la Suisse!”—was the comment from a still handsome elderly lady who had been “la compagne” of some of the founding princes of IBPC. Having experienced efficient ETH and rich MIT, what a charming folklore at the Fondation Edmond de Rothschild! Into which, like a spearhead, François tried to introduce some modern science and lab technology, as did Marianne Grunberg-Manago in the IBPC main building.

We were not rich, far from Pasteur and Jacques Monod’s USA funding, in spite of François’ immense prestige and capacity to pile up huge laboratory debts. And the equipment found at IBPC was quite “historic”. Next to bronze heads of some gentlemen, obviously to be highly respected, all kinds of curious brass-lined instruments were around: early-century balances, early microscopes, etc. The quality definition of our water-distiller was to yield “not more than 10 mg/L of residues”! Under the severe looks of Geneviève, François’ ever loyal and eternal technician/secretary and chef de cabinet, I pushed François’ notorious “aimabilité” to accept buying all sorts of expensive equipment, for instance a water distiller in quartz. Indeed, *E. coli*, bacterial and even yeast genetics had been cheaper.

To put a timer on Shiro Naono’s exclusively drop-counting fraction collector, I transformed with some copper wires an old 15 cm high old brass alarm clock, to collect my 1 meter high Sepharose-200 columns in a “heroic” approach to separate DNA/RNA hybrids. Besides Shiro, with Josette Rouviere, Donald Hayes and his wife Françoise, Georges Balassa, Denise Luzatti, Lise with Liselotte Voegelin (soon-to-be Mrs. John Richardson) and myself, we all had to cope with competition from US-based colleagues and visiting “friends”, some from Pasadena (who sometimes copied our experiments—at higher speed!)

All of us profited of François’ unending kindness, experience and critical advice. But making him spend his time on us and the lab management, we kept him from exploring experimentally his own discovery of the mRNA, and to publish a book about it. Lots of people had soon joined, and at some point up to 16 young researchers—female and male—were in

the “Gros” Laboratory—impossible to name them all. But I still see Dick Soffer pipetting acid on his writing desk, on top of books and papers, royally ignoring desperate François standing behind him, in the hope to save such a precious and expensive desk. Michel Revel was there, who had been with Howard Hiatt at Harvard doing experiments close to those we did in Jim Darnell’s lab—with less success. After a short flirt with “our” animal cell RNA, he rationally turned to the more fashionable bacterial initiation factors (keeping part of my bench!) And one day Francisco Lara, the father of Brazilian molecular biology, arrived carrying along from Sao Paulo a hundred plastic boxes with thousands of crawling worms, which I had to turn into RNA and DNA.

With all this, François still succeeded from time to time to do an experiment by himself. I admired him operating on the basis of a dynamic infrastructure, while I was totally unsuccessful to keep up my Swiss-type static lab organization, which systematically evaporated every night (Lise locked up the material for the next day’s experiments in her “garderobe”). Lots of excellent papers were produced and the lab’s postdocs, enriched by their experiences, returned to their home labs and homelands, where they more and more got important positions in research and scientific statesmanship. Of course the lambda system and *E. coli* RNA polymerase were then all and everything, whereas our studies of animal cell molecular biology were still battling on to establish some of its fundamentals.

François’ genuine interest for this coming field, as well as—more distant—that of François Jacob and Jacques Monod, and his lucidity and trust allowed us to publish work still considered as iconoclastic. “Haro—this is against the Operon Model!” was then a frequent argument. But in the red-brick tower of the rue Pierre Curie, every solid experiment and reasoning was acceptable and defended, helped by the “Pasteuriens”, the very fathers of the model. Thus, our experiments in favor of the first concept of pre-messenger RNA were published with the help of Jacques Monod, more than 12 years before the discovery of gene fragmentation into introns and exons, which made splicing and the necessity of RNA processing understandable even to a 10-years-old child.

By 1966 in a finally liberated part of the animal house, we succeeded in cultivating—in

suspension!—Hela cells (but often recovered *E. Coli!*). And François asked me—presumably since my father was an architect—to outline initial plans for the new “Gros Laboratoire à la halle aux vins”, to be established within the new, giant faculty situated place Jussieu. But then I got the proposition of Eduard Kellenberger to return to Switzerland and to work at the Swiss Cancer Institute in Lausanne (ISREC). François encouraged me to accept this offer, which led to a 7-year round-trip excursion, before I was invited by François Jacob and Raymond Dedonder (respectively, President and Director of the Institut de Biologie Moleculaire (IBM) which, finally, became the Institut Jacques Monod (IJM), to come back to France. In Lausanne I was joined by Tereza Imaizumi, an MD from Brazil, whom I first had met in Sao Paulo; later on François became her thesis adviser for a French PhD. She became my closest collaborator and later we married and had our daughter Ayalla-Mariko. Taking over the “Gros laboratoire” at Jussieu, we liberated François to assume the direction of the Institut Pasteur.

At Lausanne we had pushed forward the pre-rRNA and pre-mRNA stories. Tereza could give first proof for globin-gene sequences among the giant RNA, thanks to the newly developed cDNA technology. Having found its processing to smaller molecules, we proposed by 1973 the term “pre-mRNA” in a paper, edited by François and submitted by André Lwoff to *PNAS*. Few then supported the model of pre-mRNA and its processing into mRNA. But among them was Jim Watson: in the first edition of his textbook he put our electron-microscope pictures of giant RNA; later he stated: “... it’s called “Hn-RNA”, but should be called “pre-mRNA”, because that’s what it is!” François Gros often visited Lausanne to lecture and discuss. And François Jacob attending the meetings at CERN around Eduard Kellenberger, to found EMBO (which was financed initially by the Swiss government) also came regularly to Lausanne.

The Swiss excursion prevented me from participating in the May 1968 revolution. I only saw one Monday Liz Hansen, the Danish technician who had made the Swiss move with me, arriving all black and blue from head to feet, coming back from Paris. She had sausages instead of fingers on her hands, the result of a solid beating up along with her boyfriend in the streets around the IBPC. But I was often enough

in Paris to sense what was going on, visiting my first spouse Jutta staying in our *pied à terre* which I naively had acquired. Most impressive to me in the 1968 revolution was a sudden outspoken relation and close comradeship between the lab members, whose prior absence I had often noted and regretted; some liked it and some not—I never found out François’ feelings on that.

“Soyez réalistes — demandez l’impossible !”, written on the walls of Jussieu in Mai 1968, is also the most valid concept that leads to real progress in science. The concept of “science utile”, currently adopted by the French government, means exploring already established fields, following international trends in research which boost data production and supports carriers. Discoveries and innovation are the result of fundamental, not programmed, research. Such strategy explains the fact that, in the last 50 years, most Nobel Prizes in biology have gone to scientists in the USA, the UK, Switzerland and Germany rather than to France. And most scientific media and biotechnology became dominated by the Anglo-Saxon world.

Taking over François’ lab at Jussieu in 1973 gave us the means to explore not only the giant RNA story but also the messenger ribonucleoproteins (mRNPs), research started already in Lausanne. It was evident to me that trans-acting factors had to control not only transcription, but also RNA processing, transport and cytoplasmic regulation of mRNA. Selective repression seemed to prevail in the cytoplasmic regulation of the expression of individual mRNAs, which we found in the “ribosome-free” silent mRNPs.

Among those trans-acting factors attached to mRNA, we observed in 1970 with Nicole Granboulan uniquely structured 20S particles which later, after extensive biochemical analysis, we termed “prosome”. In an un-academic procedure and narrow interpretation of their function (but with the mediatic help of *Nature*), they now sail mostly under the term of “20S-proteasomes”, a term given several years later. The power in science of famous but naive intellectuals is ever overwhelming! The most interesting fact about the prosome-proteasome system is, indeed, their double function in regulation of protein synthesis and, as well, in selective proteolysis via the ubiquitin pathway; the latter involves the 26S proteasome complex built onto the 20S particle. But the role of the prosomes on all RNA-levels, from

chromatin to cytoplasmic mRNA, is largely ignored due to the exclusive interest in proteolysis.

What a chance to have experienced François' lab in the sixties, and all the excitement in close connection with the Pasteuriens, in real partnership with our colleagues, and often friends abroad, in particular from the USA. François also supported and attended regularly the Arolla workshops, devoted to eukaryotic molecular biology, that we had organised from our basis in Lausanne after 1973 (still surviving as an EMBO workshop!). Situated high in the mountains, it was a melting pot for researchers from the USA, Eastern and Western Europe and Asia, bringing together students and Nobel Prize winners. Sadly, much of the investments and dreams of that time have never been realized. In all these years, François' advice and support helped us go on, although at reduced levels of ambition, given the absence of sufficient financial support in France.

Carried to the highest levels of national responsibilities, spending time and effort to help his people and others at all levels, accessible to his friends and dependents, thus paying the price of his full loyalty, François never lost touch with actual science, remaining brilliant in intellectual analysis. And we all may be thankful also to Danièle who, in all these years, was the very boat that kept François afloat, and generously never refused friends to come on board when necessary.

The only point where I had a recurrent dispute over the years with François concerned "Le Système". I often said to him: "why not suggest changing this and that?" And inevitably he would say: "Ils ne vont jamais accepter !" But if logically, in the beginning the "ils" were above—right up to de Gaulle—curiously, "they" were suddenly below him; and still "ils" would not admit much change. And François would shake his head on my arguments, sometimes in anger and sometimes in friendly commiseration. Having learned over my years in France that revolutions are created by conservatives opposing organic evolution, I never accepted resignation where science is concerned. I also had to pay the price of my convictions, in particular the exclusion from the inner "family" and the professional networks. Indeed, defending unpopular concepts in science I was excluded from scientific commissions—but also rewards. Even François Jacob could not get me the *Prix fin de carrière* against the corporate system at Pas-

teur itself. Observing my frustration, François Gros suggested proposing me for *la Légion d'Honneur*; but for me only scientific recognition really mattered.

One most important change François brought about when in charge in France concerns the integration of basic science and technology, organizing the "Assises de la Recherche" in 1982. At the time of the rue Pierre Curie, the French intellectual dogma was that to work with industry was some sort of betrayal, whereas at the ETH, we were taught to eventually have to pay back to society the privilege to carry on fundamental research. Times have changed, but still in the eighties I heard one of the then "jeunes loups" at the Institut Pasteur saying in the presence of François: "... mais c'est dégeulasse de travailler avec l'industrie !" That later this brilliant fellow became a leader of French biotechnology, and that the ivory tower complex was defeated, is largely the work of François, together with Philippe Lazar. But the fundamental change of "le système" may have to wait until another politician leader, having the scope of François, may spring up in France, to render it again able to compete internationally, at the highest levels of fundamental research—the basis of innovation.

The 2017 presidential election approaching, we organized around François a small team meant to alert the candidates to the necessity of a strong program in fundamental research as the basis of innovation ensuring economic strength. Indeed, as candidates Lionel Jospin as well as Ségolène Royal had made this the first point of their political program. Our group included Isabelle Ledoux, Joseph Zyss, Reiner Veitia, Jean-Antoine Lapesant and myself; 2 members from Pasteur had left, considering our endeavor naïve. We wrote several articles and opinions of various lengths; unfortunately, our attempts to have them published by the press failed. But it was another enchanting period of collaboration with François.

François was a major personality in French and international science, as a researcher and statesman of science. I was just a minor figure in his world; sometimes I designed myself as "un clown à la cour de François le Magnifique". Thus the story told here is not of major importance; just an honest tale at the grassroots of our relation. It may amuse some of those old-timers who still survive, but also revive old

battles, in and about pioneer research at the frontiers of science. Well, I may have gone too far, talking too much about too many things; but I still have the feeling of never being able to say enough. One may just remain in admiration facing such a personality and, if I may be allowed to say, a friend as François Gros, and be thankful to fate for having been able to meet him and enjoy his concern and cordial friendship.

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